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(to be used for all correspondence after initial filing)

Application Number	09/295,463
Filing Date	April 13, 1999
First Named Inventor	Lex M. Cowsert
Art Unit	1631
Examiner Name	Marjorie A. Moran
Total Number of Pages in This Submission	
Attorney Docket Number	ISIS0231-100 (ISIS-3455)

EV513564450US

ENCLOSURES *(check all that apply)*

☒ Fee Transmittal Form

    ☐ Fee Attached

☐ Amendment / Reply

    ☐ After Final

    ☐ Affidavits/declaration(s)

☐ Extension of Time Request

☐ Express Abandonment Request

☐ Information Disclosure Statement

☐ Certified Copy of Priority Document(s)

☐ Reply to Missing Parts/ Incomplete Application

    ☐ Reply to Missing Parts under 37 CFR1.52 or 1.53

☐ Drawing(s)

☐ Licensing-related Papers

☐ Petition

☐ Petition to Convert to a Provisional Application

☐ Power of Attorney, Revocation Change of Correspondence Address

☐ Terminal Disclaimer

☐ Request for Refund

☐ CD, Number of CD(s) _____

    ☐ Landscape Table on CD

☐ After Allowance Communication to TC

☐ Appeal Communication to Board of Appeals and Interferences

☒ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)

☐ Proprietary Information

☐ Status Letter

☐ Other Enclosure(s) *(please identify below):*

Remarks

**Express Mail No. EV513564450US
Date of Deposit: February 14, 2006**

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm	Cozen O'Connor, P.C.
Signature	
Printed Name	Paul K. Legaard
Date	February 14, 2006	Reg. No.	38,534

CERTIFICATE OF TRANSMISSION/MAILING

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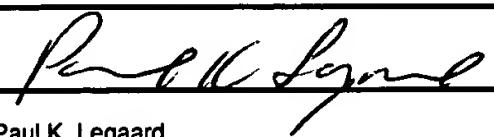| Signature	
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FEE TRANSMITTAL for FY 2005

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 250.00

Complete If Known	
Application Number	09/295,463
Filing Date	April 13, 1999
First Named Inventor	Lex M. Cowsert
Examiner Name	Marjorie A. Moran
Art Unit	1631
Attorney Docket No.	ISIS0231-100 (175393) (ISIS-3455)

METHOD OF PAYMENT (check all that apply)

☐ Check   ☐ Credit Card   ☐ Money Order   ☐ None   ☐ Other (please identify) : _____

☒ Deposit Account   Deposit Account Number: 50-1275   Deposit Account Name: Cozen O'Connor, P.C.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below   ☐ Charge fee(s) indicated below, **except for the filing fee**

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Under 37 CFR 1.16 and 1.17

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee($)	SEARCH FEES Fee($)	SEARCH FEES Small Entity Fee($)	EXAMINATION FEES Fee($)	EXAMINATION FEES Small Entity Fee($)	Fees Paid ($)
Utility	300	150	500	250	200	100	_____
Design	200	100	100	50	130	65	_____
Plant	200	100	300	150	160	80	_____
Reissue	300	150	500	250	600	300	_____
Provisional	200	100	0	0	0	0	_____

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee($)	Fee Paid ($)
_____ - or HP= _____	x _____	= _____	

HP = highest number of total claims paid for, if greater than 20.

Multiple Dependent Claims

Fee ($)	Fee Paid ($)
_____	_____

Indep. Claims	Extra Claims	Fee($)	Fee Paid ($)
_____ - or HP= _____	x _____	= _____	

HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 = _____	/ 50 = _____ (round **up** to a whole number) x		= _____

4. OTHER FEE(S)

Fees Paid ($)
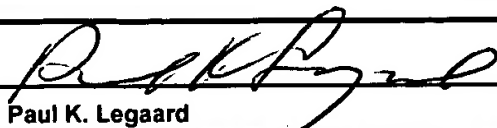
Non-English Specification, $130 fee (no small entity discount)

Other (e.g., late filing surcharge):
- Appeal Brief - $250.00   250.00

SUBMITTED BY

Signature	*[signature]*	Registration No. (Attorney/Agent)	38,534	Telephone	(215) 665-6914
Name (Print/Type)	Paul K. Legaard			Date	February 14, 2006

DOCKET NO.: ISIS0231-100 (ISIS-3455)   **PATENT**
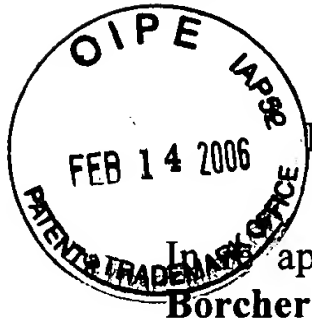
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of: **Cowsert, Baker, McNeil, Freier, Sasmor, Brooks, Ohashi, Wyatt, Borchers, and Vickers**

Confirmation No: **7206**

Serial No: **09/295,463**   Group Art Unit: **1631**

Filed: **April 13, 1999**   Examiner: **Marjorie A. Moran**

For: **Identification Of Genetic Targets For Modulation By Oligonucleotides And Generation Of Oligonucleotides For Gene Modulation**

EXPRESS MAIL INFORMATION

EXPRESS MAIL LABEL NO: **EV 513564450 us**

DATE OF DEPOSIT: **14 FEBRUARY 2006**

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APPELLANT'S APPEAL BRIEF PURSUANT TO 37 CFR §41.37(c)

Appellant hereby submits one copy of the present Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Rejection dated May 23, 2005 and the Advisory Action dated October 13, 2005 in connection with the above-identified application. A Notice of Appeal was timely filed November 17, 2005.

- 1 -

I.   Real Party In Interest

The real party in interest in the above-identified patent application is Isis Pharmaceuticals, Inc. of Carlsbad, California. An Assignment to Isis Pharmaceuticals, Inc. was recorded at Reel 010047, Frame 0285 on June 24, 1999. The real party in interest is referred to herein as "Appellant."

II.   Related Appeals And Interferences

Appellant is unaware of any related prior or pending appeal, interference, or judicial proceeding that will affect or be affected by or have any bearing on the decision rendered in this appeal.

III.   Status Of Claims

Claims 1-54, 57, 73, 77, 84, 88-98, and 103 are cancelled. Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 (i.e., all remaining claims) are pending, rejected, and now on appeal -- the appealed claims appear in the Claims Appendix.

IV.   Status Of Amendments

No amendments were made subsequent to the date of the Final Rejection.

V.   Summary Of Claimed Subject Matter

Appellant's claimed subject matter recited in claim 55 relates to a method comprising: generating *in silico* virtual compounds (see, page 7, lines 5-11) according to a thermodynamic property (see, page 16, line 26 to page 19, line 6) and at least one of targeting to functional regions of a target nucleic acid sequence (TNAS), uniform distribution to the TNAS, and combinations thereof (see, page 20, line 24 to page 22, line 2; also see, Example 2 at page 53), wherein synthetic compounds corresponding to the virtual compounds modulate the expression of the TNAS (see, page 46, line 12 to page 48, line 23); synthesizing compounds corresponding to at least some of the virtual compounds (see, page 32, line 4 to page 42, line 24); and c) robotically assaying the synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 56 relates to a method comprising: evaluating *in silico* a plurality of virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to the target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); and robotically assaying a plurality of synthetic compounds corresponding to at least some of the virtual compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 58 relates to a method comprising: generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 15, line 23 to page 16, line 25; also see, page 16, line 26 to page 19, line 6) and robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 59 relates to a method comprising: evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria comprise a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); and robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 60 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53), wherein said oligonucleotides modulate the expression of said target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence (see, page 46, line 12 to page 48, line 23); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2) and c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 62 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) robotically synthesizing a plurality of synthetic oligonucleotides having at least some of said nucleobase sequences (see,

page 32, line 4 to page 42, line 24); and c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 63 relates to a method of generating a set of oligonucleotides comprising: a) evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 64 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 65 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from target

accessibility, targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) choosing an oligonucleotide chemistry (see, page 23, line 29 to page 32, line 3); c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step a) and said oligonucleotide chemistry of step b) (see, page 32, line 4 to page 42, line 24); d) robotically assaying said set of synthetic oligonucleotides of step c) for a physical, chemical or biological activity by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22); and e) selecting a subset of said set of synthetic oligonucleotides of step c) having a desired level of physical, chemical or biological activity in order to generate said set of compounds (see, page 48, line 24 to page 50, line 2).

Appellant's claimed subject matter recited in claim 66 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) choosing an oligonucleotide chemistry (see, page 23, line 29 to page 32, line 3); c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to said thermodynamic property and said at least one other criterion, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences (see, page 16, line 26 to page 19, line 6); d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b) (see, page 32, line 4 to page 42, line 24); e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22); and f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides (see, page 48, line 24 to page 50, line 2).

Appellant's claimed subject matter recited in claim 67 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof, wherein said oligonucleotides modulate the expression of said target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53; page 46, line 12 to page 48, line 23); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); and c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 69 relates to a method of generating a set of oligonucleotides comprising: a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria comprise a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 70 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said

thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 71 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) choosing an oligonucleotide chemistry (see, page 23, line 29 to page 32, line 3); c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to said thermodynamic property and said at least one other criterion, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences (see, page 16, line 26 to page 19, line 6); d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b) (see, page 32, line 4 to page 42, line 24); e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity (see, page 47, lines 18-22); and f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides (see, page 48, line 24 to page 50, line 2).

Appellant's claimed subject matter recited in claim 72 relates to a method comprising: evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property, and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); and robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by

computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 74 relates to a method comprising: generating a library of nucleobase sequences *in silico* according to a thermodynamic property, and at least one other criterion criteria selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); and robotically assaying a plurality of synthetic oligonucleotides having said nucleobase sequences for one or more desired physical, chemical or biological properties by computer controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 75 relates to a method comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); and c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer controlled enzyme-linked immunosorbent assay (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 78 relates to a method comprising: a) evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and c) robotically assaying said

plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 79 relates to a method comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 80 relates to a method comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) choosing an oligonucleotide chemistry (see, page 23, line 29 to page 32, line 3); c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences (see, page 16, line 26 to page 19, line 6); d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c) (see, page 32, line 4 to page 42, line 24); e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 81 relates to a method comprising: evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion criteria selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); and robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 82 relates to a method comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); and c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 85 relates to a method comprising: a) evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 86 relates to a method comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property

and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and at said least one other criterion (see, page 16, line 26 to page 19, line 6); c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides (see, page 32, line 4 to page 42, line 24); and d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties (see, page 47, lines 18-22).

Appellant's claimed subject matter recited in claim 87 relates to a method comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) choosing an oligonucleotide chemistry (see, page 23, line 29 to page 32, line 3); c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c) (see, page 32, line 4 to page 42, line 24); e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity (see, page 47, lines 18-22); and f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity (see, page 48, line 24 to page 50, line 2).

Appellant's claimed subject matter recited in claim 99 relates to a method comprising: evaluating *in silico* a plurality of virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); and robotically synthesizing a plurality of synthetic

compounds corresponding to said plurality of virtual compounds (see, page 32, line 4 to page 42, line 24).

Appellant's claimed subject matter recited in claim 100 relates to a method of generating a set of oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); and c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24).

Appellant's claimed subject matter recited in claim 101 relates to a method of preparing oligonucleotides comprising: evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 16, line 26 to page 19, line 6); and robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24).

Appellant's claimed subject matter recited in claim 102 relates to a method of preparing oligonucleotides comprising: a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion criteria selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof (see, page 7, lines 5-11; page 16, line 26 to page 19, line 6; page 20, line 24 to page 22, line 2; Example 2 at page 53); b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion (see, page 16, line 26 to page 19, line 6); and c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides (see, page 32, line 4 to page 42, line 24).

VI.   Grounds of Rejection to be Reviewed on Appeal

Two grounds of rejection remain for resolution in this appeal and include:

1) whether claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are unpatentable under 35 U.S.C. §103(a) as allegedly being obvious in view of U.S. Patent No. 5,463,564 (hereinafter, the "Agrafiotis reference") in view of Uhlmann et al., Chem. Rev., 1990, 90, 543-584 (hereinafter, the "Uhlmann reference"), U.S. Patent No. 5,639,603 (hereinafter, the "Dower reference") and U.S. Patent No. 5,720,923 (hereinafter, the "Haff reference") or U.S. Patent No. 5,650,122 (hereinafter, the "Harris reference"); and

2) whether claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are unpatentable under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

VII.   Argument

A. The Combination of the Agrafiotis, Uhlmann, Dower, Haff, and Harris References (Grounds of Rejection 1)

The rejection of claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 under 35 U.S.C. §103(a) over the combination of the Agrafiotis, Uhlmann, Dower, Haff, and Harris references is improper and should be reversed because the combination of the cited references fails to produce the claimed methods.

The Final Rejection maintains that it would have been obvious to perform antisense drug design via the Agrafiotis and Uhlmann references, synthesize the compounds via the Dower reference, and perform assays via the Haff or Harris references. Appellants traverse the rejection and respectfully request reversal.

Each of Appellants claims recites a minimum of two steps: first, each claim recites generation *in silico* of virtual compounds or a library of nucleobase sequences and/or evaluation a plurality of virtual compounds or oligonucleotides according to a thermodynamic property and at least one of targeting to functional regions of a target nucleic acid sequence, uniform distribution to the target nucleic acid sequence, and combinations thereof; second, each claim recites synthesis of compounds or oligonucleotides corresponding to at least some of the virtual compounds and/or robotically assaying the synthetic compounds or oligonucleotides for one or more desired physical, chemical or biological properties. Thus, each of Appellants claims recites generation or evaluation of *in silico* or virtual compounds according to defined criteria **prior** to their synthesis or assay.

In contrast, the methods reported in the Agrafiotis reference **begin** with the **actual** synthesis of members of the physical library (see, column 5, lines 31-45) prior to testing the totality of the physical library members for a desired property (see, column 5, line 57 to column 6, line 21). The Agrafiotis methods next select a subset of the physical members of the physical library to generate their virtual libarary and subsequent synthesis instructions (see, column 6, lines 22-48). Figures 3-6 of the Agrafiotis reference embody this methodology. Appellants are unable to locate any portion of the Agrfiotis reference that teaches 1) generation *in silico* of virtual compounds or a library of nucleobase sequences and/or evaluation a plurality of virtual compounds or oligonucleotides according to a thermodynamic property and at least one of

targeting to functional regions of a target nucleic acid sequence, uniform distribution to the target nucleic acid sequence, and combinations thereof; and 2) synthesis of compounds or oligonucleotides corresponding to at least some of the virtual compounds and/or robotically assaying the synthetic compounds or oligonucleotides for one or more desired physical, chemical or biological properties. That is, Appellants are unable to locate any portion of the Agrfiotis reference that teaches generation or evaluation of *in silico* or virtual compounds according to defined criteria **prior** to their synthesis or assay.

The Final Rejection asserts at page 5 that the Agrafiotis reference reports "analysis of physical and/or electronic property data related to his generated compounds" and that "his synthesis generator uses a combination of data including structural, electronic and physiochemical, and receptor fit criteria" and thus teaches using thermodynamic criteria with other criteria. The portions of the Agrafiotis reference relied upon in the Office Action, however, do not support this conclusion.

For example, column 11, lines 57-65 of the Agrafiotis reference report that the analysis robots may additionally include a physical and/or electronic property analysis module(s) which "analyzes the compounds synthesized by the Chemical Synthesis Robot" to obtain physical and/or electronic property data related to the compounds. Thus, this portion of the Agrafiotis reference relied upon in the Office Action supports the notion of obtaining physical and/or electronic property data related to the actual compounds already synthesized, and not to using thermodynamic criteria with other criteria to generate *in silico* compounds.

Column 12, lines 10-47 of the Agrafiotis reference report a reagent database 120 and a structure-activity database 122. These databases contain data regarding the reagents in the Reagent Repository as well as Structure-Activity data, respectively. The Structure-Activity data is obtained as a result of the analysis of the compounds performed by the analysis robots. Nowhere does this portion of the Agrafiotis reference teach using thermodynamic criteria with other criteria to generate *in silico* compounds. The fact that the databases reported in the Agrafiotis reference may be in a computer readable format does not mean that the compounds produced by using thermodynamic criteria with other criteria are also *in silico* compounds. Indeed, it appears that these two databases are used for the actual generation of real compounds.

Lastly, column 16, line 60 to column 17, line 2 reports that the Synthesis Protocol Generator 104 uses several parameters to generate an initial Directed Diversity Chemical Library, which is a library of real compounds. Nowhere does this portion of the Agrafiotis reference teach using thermodynamic criteria with other criteria to generate *in silico* compounds.

None of the additional references (*i.e.*, Uhlmann, Dower, Haff, and Harris references) cure the deficiencies of the Agrafiotis reference, nor are they alleged to in the Final Rejection.

Appellants respectfully submit that the references, alone or in combination, fail to teach or suggest the claimed methods. In view of the foregoing, Appellants respectfully request that the rejection of claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 under 35 U.S.C. § 103(a) over the combination of the Agrafiotis, Uhlmann, Dower, Haff, and Harris references be reversed.

B. The New Matter Rejection (Grounds of Rejection 2)

Claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Appellants traverse the rejection and respectfully request reconsideration because the specification provides ample written description supporting the claimed inventions.

The Final Rejection asserts at page 3 that "the step of generating oligonucleotide sequences is performed BEFORE any step of calculating thermodynamic properties or scores," thus there is no support for generating an *in silico* compound of any kind according to a thermodynamic property, whether in combination with another property or alone. Appellants disagree.

As a preliminary matter, Appellants do not disagree with the notion that a target nucleic acid (the term chosen by the Examiner is "oligonucleotide") sequence is selected or provided (the term chosen by the Examiner is "generated") prior to the calculating thermodynamic properties. Indeed, Appellants' specification teaches:

> The present invention is directed to iterative processes for defining
> chemical compounds with prescribed sets of physical, chemical and/or
> biological properties, and to systems for implementing these processes.
> During each iteration of a process as contemplated herein, a target

> nucleic acid sequence is provided or selected, and **a library of (candidate) virtual compounds is generated** *in silico* (that is in a computer manipulatible and reliable form) **according to defined criteria**. A library of virtual compounds is generated. These virtual compounds are reviewed and compounds predicted to have particular desired properties are selected. The selected compounds are synthesized, preferably in a robotic, batchwise manner; and then they are robotically assayed for a desired physical, chemical or biological activity in order to identify compounds with the desired properties. Active compounds are, thus, generated and, at the same time, preferred sequences and regions of the target nucleic acid that are amenable to modulation are identified. (emphasis added).

(See, page 7, lines 5-17 of the specification). Thus, Appellants quite clearly teach provision or selection of a target nucleic acid sequence, followed by **generation** of a library of virtual compounds *in silico* according to defined criteria.

The numerous criteria that can be used to generate the virtual compounds are set forth in step 300, and all sub-steps therewithin, set forth in Figures 4 and 5. For example, oligonucleotide length (step 302; see page 16, line 13), thermodynamic, sequence, and homology scores (step 306; see page 16, lines 29-30), other thermodynamic and kinetic properties (step 317; see page 17, lines 8-11), target accessibility factors (steps 324-341; see page 19, lines 16-27), homology scores (step 342; see page 20, lines 8-17), targeting functional regions (step 349; see page 20, line 25 to page 21, lines 7), and uniform distribution of oligonucleotides (step 375; see page 21, lines 17-30) can be used to generate the virtual compounds. Thus, one skilled in the art is taught to undertake these considerations when generating a virtual library of compounds. The end result of all these considerations is the generation of a library of virtual compounds, wherein each of the compounds comprise desired properties or defined criteria. Further, once these considerations have been made (ending with step 380 or step 385), Appellants teach that the oligonucleotide sequences are passed onto step 400 where oligonucleotide chemistries are assigned (see page 21, line 30 to page 22, line 2) and then to step 500 where the compounds are synthesized.

An apparent confusion between "generating oligonucleotide sequences" and "generating an *in silico* compound" recited in the Final Rejection may be at the crux of the rejection. It is quite true that one skilled in the art may generate oligonucleotide sequences prior to, for example, calculating thermodynamic properties, targeting to functional regions of a target

nucleic acid sequence, or uniform distribution to the target nucleic acid sequence, and combinations thereof. This not does mean, however, that *in silico* compounds are not generated according to a thermodynamic property. Indeed, it is upon carrying out such criterion recited in the claim that one skilled in the art can "generate *in silico* **compounds**" (as opposed to generating oligonucleotide sequences). Generating oligonucleotide sequences simply serves as a convenient starting point, for example, along with many other criteria, such as those recited in the claim, for generating *in silico* "**compounds**." Indeed, steps 300 and 400, and desired criterion thereunder, are carried out to generate *in silico* "**compounds**" (see, for example, page 15, line 24 to page 32, line 3 of the specification). Thus, an end result to carrying out the criterion recited in the claim is the generation of "*in silico* **virtual compounds**" as recited in claim 55, for example. Thus, there is ample support in the specification for the recited claims.

The Final Rejection also asserts at page 3 that the assessment of a compound for a criterion such as hybridization (i.e., targeting) is "performed separately from the thermodynamic property calculations" and suggests that they cannot be performed in combination as claimed. The Examiner, however, appears to misunderstand the claims. Claim 55, for example, recites that the method comprises generating *in silico* virtual compounds according to a thermodynamic property and at least one of targeting to functional regions of a target nucleic acid sequence, uniform distribution to the target nucleic acid sequence, and combinations thereof. Thus, the claim recites that the *in silico* virtual compounds are generated according to a thermodynamic property **and** either 1) targeting to functional regions of a target nucleic acid sequence **or** 2) uniform distribution to the target nucleic acid sequence, **or** 3) targeting to functional regions of a target nucleic acid sequence and uniform distribution to the target nucleic acid sequence (the combination thereof). Further, the specification does not limit the consideration of targeting to functional regions of a target nucleic acid sequence or uniform distribution to the target nucleic acid sequence to take place either before or after the calculation of thermodynamic properties.

In view of the foregoing, Appellants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly failing to provide sufficient written description be withdrawn.

VIII. Claims Appendix

The following claims are on appeal:

55. A method comprising:

a) generating *in silico* virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof, wherein synthetic compounds corresponding to said virtual compounds modulate the expression of said target nucleic acid sequence;

b) synthesizing compounds corresponding to at least some of said virtual compounds; and

c) robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

56. A method comprising:

evaluating *in silico* a plurality of virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

58. A method comprising:

generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and

robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

59.   A method comprising:

evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria comprise a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties.

60.   A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof, wherein said oligonucleotides modulate the expression of said target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer controlled enzyme-linked immunosorbent assay.

61.   The method of claim 60 wherein said target nucleic acid sequence is genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

62.   A method of generating a set of oligonucleotides comprising:

        a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

        b) robotically synthesizing a plurality of synthetic oligonucleotides having at least some of said nucleobase sequences; and

        c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

63.   A method of generating a set of oligonucleotides comprising:

        a) evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

        b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

        c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

64.   A method of generating a set of oligonucleotides comprising:

        a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

        b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

65.   A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from target accessibility, targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) choosing an oligonucleotide chemistry;

c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step a) and said oligonucleotide chemistry of step b);

d) robotically assaying said set of synthetic oligonucleotides of step c) for a physical, chemical or biological activity by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay; and

e) selecting a subset of said set of synthetic oligonucleotides of step c) having a desired level of physical, chemical or biological activity in order to generate said set of compounds.

66.   A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to said thermodynamic property and said at least one other criterion, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

67.   A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof, wherein said oligonucleotides modulate the expression of said target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

68.   The method of claim 67 wherein said target nucleic acid sequence is genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

69.   A method of generating a set of oligonucleotides comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria comprise a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

70.   A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

71.   A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to said thermodynamic property and said at least one other criterion, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

72.   A method comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property, and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

74.   A method comprising:

generating a library of nucleobase sequences *in silico* according to a thermodynamic property, and at least one other criterion criteria selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and

robotically assaying a plurality of synthetic oligonucleotides having said nucleobase sequences for one or more desired physical, chemical or biological properties by computer controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

75.   A method comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer controlled enzyme-linked immunosorbent assay.

76.   The method of claim 75 wherein said nucleic acid sequence genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

78.   A method comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

79.   A method comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

80.   A method comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

81.   A method comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion criteria selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

82.   A method comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

83.   The method of claim 82 wherein said nucleic acid sequence is genomic DNA, cDNA, product of a polymerase chain reaction, expressed sequence tag, mRNA or structural RNA.

85.   A method comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

86.   A method comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and at said least one other criterion;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

87.   A method comprising:

a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

99.   A method comprising:

evaluating *in silico* a plurality of virtual compounds according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to target nucleic acid sequence, and combinations thereof; and

robotically synthesizing a plurality of synthetic compounds corresponding to said plurality of virtual compounds.

100.   A method of generating a set of oligonucleotides comprising:

        a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

        b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion; and

        c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

101.   A method of preparing oligonucleotides comprising:

        evaluating *in silico* a plurality of virtual oligonucleotides according to a thermodynamic property and at least one other criterion selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof; and

        robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides.

102.   A method of preparing oligonucleotides comprising:

        a) generating a library of nucleobase sequences *in silico* according to a thermodynamic property and at least one other criterion criteria selected from targeting to functional regions of a target nucleic acid sequence, uniform distribution to said target nucleic acid sequence, and combinations thereof;

        b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to said thermodynamic property and said at least one other criterion; and

        c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

IX.   Evidence Appendix

None.

X.   Related Proceedings Appendix

None.

Conclusion

All rejections of the pending claims are improper and should be reversed. For the reasons given above, appealed claims 55, 56, 58-72, 74-76, 78-83, 85-87, and 99-102 are patentable.

Respectfully submitted,

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